Modeling hippocampal neurogenesis using human pluripotent stem cells.

Journal: Stem Cell Reports

Publication Year: 2014

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PubMed link: 24672753

Funding Grants: Development of Induced Pluripotent Stem Cells for Modeling Human Disease

Public Summary:
Since hippocampal DG neurons have been thought to be involved in Schizophrenia (SCZD), we applied our protocol to SCZD patient-derived stem cells to see if we can uncover important clues as to the roles that these cells may play in the disease. We found that DG neurons generated from SCZD patient-derived stem cells exhibited significantly lower levels of key proteins that are crucial for neuronal development , resulting in reduced neuronal activity, and potentially causing the cognitive deficits clinically observed in these patients. Our approach offers important insights into the neurodevelopmental aspects of SCZD and may be a promising tool for drug screening and personalized medicine.

Scientific Abstract:
The availability of human pluripotent stem cells (hPSCs) offers the opportunity to generate lineage-specific cells to investigate mechanisms of human diseases specific to brain regions. Here, we report a differentiation paradigm for hPSCs that enriches for hippocampal dentate gyrus (DG) granule neurons. This differentiation paradigm recapitulates the expression patterns of key developmental genes during hippocampal neurogenesis, exhibits characteristics of neuronal network maturation, and produces PROX1+ neurons that functionally integrate into the DG. Because hippocampal neurogenesis has been implicated in schizophrenia (SCZD), we applied our protocol to SCZD patient-derived human induced pluripotent stem cells (hiPSCs). We found deficits in the generation of DG granule neurons from SCZD hiPSC-derived hippocampal NPCs with lowered levels of NEUROD1, PROX1, and TBR1, reduced neuronal activity, and reduced levels of spontaneous neurotransmitter release. Our approach offers important insights into the neurodevelopmental aspects of SCZD and may be a promising tool for drug screening and personalized medicine.